

Three from Seattle

Encouraging results from clinical trials of the experimental antiretrovirals TAF, fostemsavir, and BMS-955176 are presented at the 2015 Conference on Retroviruses and Opportunistic Infections

By Tim Horn

By 2025, antiretroviral treatment could be as different from that used today as triple therapy in 1997 was from AZT monotherapy in 1987. Maybe even as evolved as the once-daily and single-pill regimens of 2015 compared with the multi-dose, multi-pill regimens of 1997. A lot can be achieved in 10 years. However, this is largely dependent on setting ambitious goals. It also means making sure that all groups with vested interests in HIV treatment—including people living with HIV, health care providers, researchers, and pharmaceutical companies—remain fully engaged in this effort.

We need to push technology to manufacture new compounds that not only are effective at controlling HIV, but also have fewer toxicities, less complicated dosing, and hold promise for people living with drug-resistant virus and are in desperate need of new treatment options. Novel therapies also need to be brought to market at prices that are affordable.

Research updates for three promising HIV drugs in development were showcased at the 2015 Conference on Retroviruses and Opportunistic Infections, held in February in Seattle.

Tenofovir alafenamide fumarate (TAF)

TAF works very much like its predecessor tenofovir disoproxil fumarate (TDF), the active ingredient in Viread and a component of Truvada, Atripla, Complera, and Stribild. The difference is the way in which they are converted to the active drug—tenofovir—in the body. Whereas TDF undergoes its conversion in the bloodstream, TAF undergoes its conversion inside cells. The advantages of this are threefold:

1. The dose of TAF (25 mg; 10 mg when used with certain drugs) is much lower than that of TDF (300 mg).
2. The much lower amounts of tenofovir in the blood means less drug will travel to the kidneys and bones and have damaging effects, which has been a problem for many people living with HIV using regimens containing TDF.
3. The amount of tenofovir inside cells is approximately seven times higher with the use of TAF compared with TDF. Test tube studies have suggested this might render TAF effective against HIV that has become at least partially resistant to tenofovir while taking TDF.

TAF is being developed as a replacement for TDF in Stribild, Complera, and Truvada, and as a component of a new combination tablet that will also contain the protease inhibitor Prezista (darunavir), the boosting agent Tybost (cobicistat), and the nucleoside analog Emtriva (FTC).

In separate presentations at CROI 2015, Dr. David Wohl of the University of North Carolina and Dr. Paul Sax of Harvard Medical School presented results of efficacy and safety analyses using combined data from two Phase III studies comparing Stribild (elvitegravir/cobicistat/FTC/TAF) to the new tablet containing TAF instead of TDF (referred to as E/C/F/TAF, for short, by researchers).

In total, 867 people living with HIV received Stribild in these two studies; 866 received the new quad tablet. Most were men (85%) and 39 percent were either black or Hispanic/Latino. At the start of the study, CD4 counts averaged 405 cells and viral loads averaged 38,000 copies/mL. Approximately 12 percent had CD4 counts below 200 and 23 percent had viral loads above 100,000 copies/mL. Evaluating how well treatment regimens work in people with suppressed immune systems and high viral loads is very important.

After nearly a year of treatment (48 weeks), 92% of those in the E/C/F/TAF group, compared with 90% of those in the Stribild group, had undetectable viral loads (below 50 copies/mL). This small difference was not statistically significant, meaning that it could have been due to chance. More than 90 percent of people in both groups who entered the trial with high viral loads had undetectable viral loads at the 48-week time point.

Increases in CD4 counts were better in the E/C/F/TAF group (+211 cells), compared with the Stribild group (+181 cells). This difference was statistically significant.

Moderate-to-severe side effects were rare, occurring in approximately 1% of study volunteers in both groups, as were side effect-related treatment discontinuations. Diarrhea was the most common side effect (18%), followed by nausea (16%), and headache (13%).

A review of kidney-related toxicities favored TAF. For starters, of the four volunteers who discontinued treatment because of kidney-related problems, all were among those taking TDF-inclusive Stribild. Decreases in estimated glomerular filtration rate (eGFR)—a marker that uses blood creatinine levels to detect kidney damage—were more pronounced in the Stribild group compared with the E/C/F/TAF group. Tests of excess protein excretion by the kidneys (proteinuria), including protein, albumin, retinol binding protein, and beta-2 microglobulin, also pointed to a clear advantage of TAF over TDF.

Decreases in bone mineral density (BMD), measured using DEXA scans, were more pronounced in the Stribild group compared with the E/C/F/TAF group.

Though there was evidence of spine and hip BMD loss in both groups, the decreases were significantly more pronounced in the Stribild group.

Study volunteers in the E/C/F/TAF group experienced greater increases in their triglyceride, total cholesterol, “bad” LDL cholesterol, and “good” HDL cholesterol compared with those in the Stribild group. The likely reason for this is that tenofovir has lipid-lower effects in the body, and with much less of it circulating in the bloodstream with the use of TAF versus TDF, the lipid-lowering effect is lost. However, it’s not at all clear whether this means that TAF-treated individuals face a higher risk of cardiovascular disease (CVD) compared with TDF-treated individuals, given that HDL cholesterol levels, which help to negate the effects of “bad” LDL cholesterol, also increased. In fact, ratios of total cholesterol to HDL cholesterol—an indicator of lipid health—were the same in both groups.

Several other E/C/F/TAF study results were presented at CROI 2015. These include a 48-week study, reported by Dr. Anton Pozniak of Chelsea & Westminster Hospital in London, exploring the safety of E/C/F/TAF for use among people living with HIV mild-to-moderate renal impairment, defined as a creatinine clearance rate of 30mL/min or higher. The study included 242 individuals with mild-to-moderate kidney impairment whose treatment regimens were switched from both TDF- and non-TDF-containing regimens to E/C/F/TAF. According to Dr. Pozniak’s report, 92% of the study participants maintained undetectable viral loads at the 48-week follow-up time point and, importantly, there was no change in eGFR results and significant improvements in other markers of kidney function. Improvements in BMD measurements were also documented.

Only long-term data from ongoing studies will confirm whether TAF has a better kidney and bone side effect profile or a worse CVD profile.

Fostemsavir

Fostemsavir is one of two drugs being developed by Bristol-Myers Squibb (BMS) that have helped to fill a serious gap in the HIV treatment pipeline: experimental agents that hold tremendous potential for people with cross-class resistant HIV and who are in need of regimens containing new agents. The other drug, BMS-955176, is discussed below.

Fostemsavir, formerly known as BMS-663068, is an attachment inhibitor. Other drugs in this broad class include Selzentry (maraviroc) and Fuzeon (enfuvirtide). Fostemsavir works differently than these drugs. Fostemsavir is another agent that undergoes conversion in the body, in this case to the active drug BMS-626529. It works by binding directly to the HIV gp120 protein and thereby prevents initial attachment of the virus to CD4 cells.

Though fostemsavir is active against HIV that targets either the CCR5 or CXCR4 co-receptors on CD4 cells—unlike Selzentry, which is only active against CCR5-targeting virus—fostemsavir may be of limited use for people with HIV with resistance mutations to the BMS-626529, which do not appear to be the result of prior treatment experience. Monogram Biosciences has a laboratory test that can demonstrate whether a person's HIV has limited or no susceptibility to the BMS-626529.

Results from a Phase 2b clinical trial of fostemsavir were reported by Dr. Carey Hwang of BMS at CROI 2015. The study enrolled 251 treatment-experienced people living with HIV and randomized them to receive one of four doses of the drug—400 mg or 800 mg twice-daily, or 600 mg or 1,200 mg once-daily—in combination with Viread (TDF) and the integrase inhibitor Crixivan (raltegravir). A control group of people taking ritonavir-boosted Reyataz (atazanavir) plus TDF and raltegravir was also included in the study. All study volunteers had susceptibility results which indicated that BMS-626529 was effective against their HIV. Roughly 6% of those who screened for the study were excluded because their virus was not susceptible to BMS-626529.

Approximately 60% of the study participants were male and 38% were white. At study entry, the average viral load was 75,000 copies/mL and the average CD4 count was 230 cells. More than 40% had viral loads above 100,000 copies/mL and nearly 40% had CD4 counts below 200 cells.

Through week 48, rates of undetectable viral loads (below 50 copies/mL) were generally similar across all fostemsavir groups—between 61% and 82%—and did not appear to differ considerably compared to the virologic response rate in the Norvir (ritonavir)-boosted Reyataz (atazanavir) group (71%). CD4 count increases were also comparable across all study groups.

Study volunteers with high viral loads at the start of the study had comparable 48-week viral load suppression rates, compared with those with lower viral loads, regardless of which treatment group they were in. Viral load responses were also similar among those in different pre-treatment fostemsavir. All fostemsavir doses were generally well tolerated with no major safety concerns in any of the dosing groups.

In light of these and other positive results, a Phase III clinical trial of fostemsavir among heavily treatment-experienced patients began in February. For the purposes of the Phase III trial, heavily treatment-experienced patients are defined as individuals who can no longer formulate a viable regimen (standard three-drug treatment regimen) due to accumulation of drug resistance, side effects, and/or drug-drug interactions. The fostemsavir dose that has been selected for this study is 600 mg, taken twice daily.

The hope is that fostemavir will turn out to help heavily treatment-experienced patients with little or no other treatment options, though all efforts should be made to combine it with drugs that are at least partially active against HIV.

BMS-955176

BMS-955176 is a maturation inhibitor, inhibiting one of the last steps of HIV's life cycle, ultimately causing CD4 cells to release immature and non-infectious virus particles. It follows another maturation inhibitor, bevirimat, discontinued in 2010. Though bevirimat had fairly robust potency against HIV, it did not work well for a sizeable population of people with a naturally occurring mutation in HIV (codon 370 in Gag).

According to the Phase IIa study results presented at CROI 2015 by Dr. Melanie Thompson of the AIDS Research Consortium of Atlanta, BMS-955176 demonstrated antiviral activity in the presence of pre-treatment HIV mutations not responsive to bevirimat. The drug achieved maximum viral load drops of 1.70 log copies/mL—similar to that seen in Phase II studies of bevirimat—at a dose of 40 mg once daily, with viral load reductions leveling off at around 1.64 log copies/mL below pre-treatment levels after the tenth and final dose. The viral load reductions were sustained for approximately one week after the drug was discontinued.

The study enrolled 60 HIV-positive individuals, the vast majority of whom were white men who had not previously used any HIV medications. In addition to the 40 mg dose, doses of 5, 10, 20, 80 and 120 mg were evaluated. Approximately eight people received one of the six maturation inhibitor doses; two volunteers in each dosing group received placebo.

Possible side effects, occurring in at least 5% of study participants, included headache, abnormal dreams, night sweats, and diarrhea. However, most of these side effects were just as likely to be documented in those receiving placebo.

A Phase IIb study is expected to open soon. It plans to further explore BMS955176's efficacy and safety.

More treatment options, especially from new drug classes, are always welcome. Stay tuned for more information on new treatment options as they make their way through the drug development pipeline.